Clinical Study Protocol

CM 2017-01

Phase 1 Study Using a Plasmid DNA Coding for Emm55 Streptococcal Antigen in Patients with Unresectable Stage III or Stage IV Cutaneous Melanoma

Protocol Identifying Number:	CM 2017-01
Principal Investigator:	Joseph Markowitz, MD, PhD
IND Sponsor:	Morphogenesis, Inc.
Funded By:	Morphogenesis, Inc.
Draft/Version Number:	Version 7; September 1, 2020
NCT Number:	03655756

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE(s)	Adverse Event(s)
AGE	Agarose Gel Electrophoresis
ANOVA	Analysis of Variance
APC	Antigen Presenting Cells
aPTT	activated Partial Thromboplastin Time
BOR	Best Overall Response
CBC	Complete Blood Count
CD	Cluster of Differentiation
CFR	Code of Federal Regulations
CMP	Comprehensive Metabolic Panel
CR	Complete Response = complete regression of all lesions
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
DCR	Disease Control Rate
DLT	Dose-limiting Toxicity
DM	Data Management
DMF	Drug Master File
EBV	Epstein-Barr Virus
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF(s)	electronic Case Report Form(s)
E. coli	Escherichia coli
EtBr	Ethidium Bromide (DNA stain)
FTA	Fluorescent Treponemal Antibody
GAPDH	Glyceraldehyde 3-Phosphate Dehydrogenase
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEK293T	Human Embryonic Kidney cells
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HTLV	Human T Lymphotropic Virus 1 & 2
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IHC	Immunohistochemistry
IFx-Hu2.0	pAc/emm55 DNA plasmid combined with in vivo-jetPEI® in the presence of glucose
INFγ	Interferon Gamma

IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
LTF	Lost to Follow Up
MCB	Master Cell Bank
MHC	Major Histocompatibility Complex
MM	Medical Monitor
NED	No Evidence of Disease
OD	Optical Density
ORR	Overall (Objective) Response Rate
OS	Overall Survival
pAc/*emm55*	DNA plasmid encoding the emm55 gene
pAc/empty	pAc/emm55 DNA plasmid without the emm55 gene
PBRS	Peachtree Bioresearch Solutions, Inc.
PBS	Phosphate Buffered Saline
PCR	Polymerase Chain Reaction
PD	Progressive Disease = ≥ 20% increase in tumor burden
PD-1	Programmed Cell Death Protein 1
PE	Phycoerythrin
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PI	Principal Investigator
PT	Prothrombin Time
PR	Partial Response = ≥ 30% decrease in tumor burden
QC	Quality Control
RAB-AP01	Anti-Emm55 Rabbit Polyclonal Antibody
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RPR	Rapid Plasmin Reagin
RTPCR	Reverse Transcriptase Polymerase Chain Reaction
SAE(s)	Serious Adverse Event(s)
SC	Subcutaneous
SCB	Starter Cell Bank
SEM	Standard Error of the Mean
SD	Stable Disease = % change in tumor burden is between -30% and +20%
SOP	Standard Operating Procedure
S. pyogenes	Streptococcus pyogenes
SumL	Sum of the Longest Diameters
TCR	T Cell Receptor
TE	10 mM Tris-Cl, pH 8.0, 1 mM Ethylenediaminetetraacetic acid
TEAE(s)	Treatment-emergent adverse event(s)
UP(s)	Unexpected Adverse Drug Experience
VCOG	Veterinary Cooperative Oncology Group
WCB	Working Cell Bank

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: _____

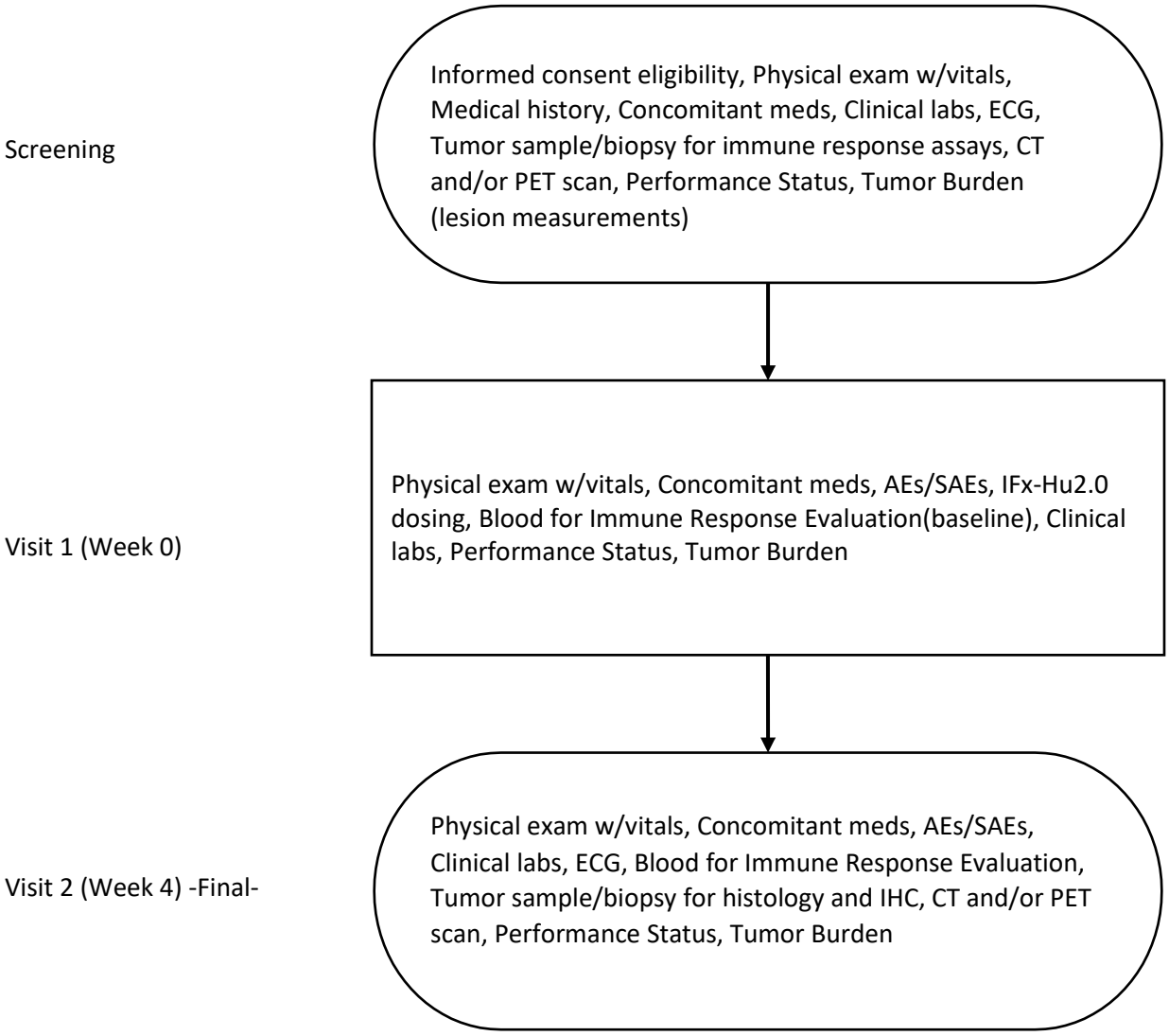
Signature: _____ Date: _____

PROTOCOL SUMMARY

Title	Phase 1 Study Using a Plasmid DNA Coding for Emm55 Streptococcal Antigen in Patients with Unresectable Stage III or Stage IV Cutaneous Melanoma
Short Title	pDNA Intralesional Cancer Vaccine for Cutaneous Melanoma
Protocol Number	Melanoma 2017-01
Phase	Phase 1
Methodology	Non-randomized, open-label, uncontrolled
Study Duration	Approximately 1 year
Study Center(s)	Single-center
Objectives	Primary: To assess safety and feasibility Secondary: To assess any antitumor response
Number of Subjects	Six
Diagnosis and Main Inclusion Criteria	Male or female, confirmed stage III or stage IV unresectable melanoma with lesions accessible for intralesional injection
Study Product, Dose, Route, Regimen	Plasmid DNA encoding a Streptococcal antigen in a cationic polymer-based solution in doses of 100 µg delivered intralesionally at a single time point "Week 0" with a maximum of three lesions injected. The primary endpoint (DLT) will be assessed at 4 weeks.
Optional dosing	After primary endpoint has been met (DLT), at the investigator's discretion in consultation with the sponsor, patients may receive additional doses on a 3-week cycle.
Follow-up - Primary	Week 4; Day 28+/-7 business days.
Follow-up – Optional.	21 days +/- 7 business days from last dose administered.
Follow-up – Long-term	Obtain OS/subsequent treatments for melanoma after MCC 19500 as of 11/16/2020 for all patients with clinical response if available.
Study Procedures	Six patients will receive IFx-Hu2.0 on an outpatient basis at a single time point in a single lesion, two lesions, or three lesions, as a monotherapy (a maximum of three lesions could be injected). These patients will be assessed for any immediate adverse reactions and at Week 4 (Day 28+/-7 business days) for any delayed adverse events. After the primary endpoint has been met (DLT), patients may receive additional doses on an optional 3-week cycle.
Duration of Administration	Single time point with option for additional doses
Potential Risks	Other cancer vaccine trial results have reported patients experiencing reactions such as mild fever, skin reactions, sweats and chills, which are often described as "flu-like" symptoms.
Reference Therapy	None

Statistical Methodology	The data analysis is described to assess the safety of the injection of the study agent in six patients The intention-to-treat approach will be used for response to treatment data analysis of this trial (secondary objective). The exploratory testing will be mainly descriptive in this pilot set of patients

SCHEMATIC OF STUDY DESIGN



Note: If patient consents to additional treatment, this may be performed every three weeks with a 21-day follow-up visit.

1. KEY ROLES

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2. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Chen and Mellman described what they termed the Cancer-Immunity Cycle, a series of stepwise events that must be carried out for an effective anticancer immune response to occur (Chen and Mellman 2013). These events must be initiated, allowed to proceed and then to expand. In the first step of this process neoantigens created by the accumulation of genetic alterations during oncogenesis must be released and captured by antigen presenting cells (APC), a process that must be accompanied by specific signals such as cytokines. We plan to optimize cancer immunity by intervening at the first step of the cycle.

Emm55 is a serotyping protein normally expressed on the surface of the bacterium *Streptococcus pyogenes* (*S. pyogenes*) and is highly antigenic (Glikin and Finocchiaro 2014, Ramiya, Jerald et al. 2014). Intralesional injection of a novel plasmid DNA vaccine expressing the Emm55 protein derived from *S. pyogenes* showed clinical efficacy in an equine metastatic melanoma (Ramiya, Jerald et al. 2014). By utilizing a bacterial (foreign) antigen, it is possible to expose 'self' tumor antigens and overcome tolerance to them, regardless of their number or uniqueness. This can be done by transfecting the pAc/*emm55* plasmid into tumor cells *ex vivo* and administering the resultant 'personalized' whole-cell vaccine as an intradermal injection. It is also possible to create a 'personalized' vaccine by injecting the pAc/*emm55* plasmid DNA directly into a patient's lesion. In this way, an immune response is initiated to the neoantigens relevant to each individual patient without the difficulties involved in developing individualized targeted therapies.

The product being tested in this clinical study, IFx-Hu2.0, is a plasmid DNA, pAc/*emm55*, formulated with *in vivo*-jetPEI®, a cationic polymer that aids in cellular uptake of DNA, will be administered by intralesional injection. IFx-Hu2.0 is a cancer immunotherapy that stimulates the immune system to fight cancer. When introduced into a patient's tumor cells, pAc/*emm55* drives expression of the highly immunogenic Emm55 protein in the cytoplasm and on the surface of the tumor cells. In this protocol, IFx-Hu2.0 will be utilized as a monotherapy in a feasibility study prior to combining it with checkpoint blockade.

Cancer immune evasion transpires when two events occur: 1) immune surveillance fails to recognize the alterations and abnormalities of tumors and 2) tumors take advantage of inhibitory pathways which are hardwired into the immune system for avoiding autoimmunity (Chen and Mellman 2013). Surface expression of the Emm55 antigen through intralesional injection of pAc/*emm55* engages the patient's immune system and thwarts the tumor's ability to evade surveillance by exposing multiple patient-specific tumor antigens and activating a wide array of naïve T cells.

IFx-Hu2.0 primes the immune response to a broad array of patient-specific tumor antigens. Due to the antitumor response being directed specifically against abnormal tumor proteins, there have been no reported side effects associated with this therapy. However, when breaking tolerance to tumor-associated antigens, which are 'self' antigens, there is a possibility of inducing some form of

autoimmunity. Patients receiving other cancer vaccine therapies have experienced reactions including mild fever, skin reactions, sweats and chills, tachypnea and hypotension.

2.2 Rationale

The Emm55 Antigen

M proteins, the cell surface antigens responsible for the M serospecificities of *S. pyogenes*, are encoded by *emm* genes. Emm55 is one of hundreds of M proteins. Anchored in the *S. pyogenes* cell wall, M proteins mediate adhesion to host cells and connective tissues as well as bacterial cell invasion. M proteins act as antiphagocytic factors which are crucial for defense against human innate immunity (Nitsche-Schmitz, Rohde et al. 2007). Due to high variability at the N-terminal region of M proteins, there have been more than 200 distinct types recorded in public databases. M proteins have been considered as vaccine candidates against group A Streptococcal-mediated strep throat and suppurative skin diseases (Dale, Smeesters et al. 2017). However, some M proteins bind collagen and may cause side effects such as acute rheumatic fever in humans through molecular mimicry of collagen (Dinkla, Nitsche- Schmitz et al. 2007). Emm55, though, has been shown not to bind collagen due to the conformational influences of flanking sequences (Reissmann, Gillen et al. 2012). In the IFx-Hu2.0 vaccine, the Emm55 protein acts as an immunologic priming antigen aimed at attracting the patient's immune system to tumor cells.

The product being tested in this clinical study, IFx-Hu2.0, is designed to exploit the inherent vulnerability of specific differences from patient to patient, lesion to lesion, and cell to cell. Regardless of the degree of complexity of an individual's antigenic signature, this truly patient-specific approach capitalizes on the antigenic differences to create the broadest immune response possible. By introducing the *emm55* gene from *S. pyogenes* into a patient's tumors by intralesional injection, the highly immunogenic Emm55 protein is expressed on tumor cells and initiates an immune cascade leading to the activation of multiple immune cells, including cytotoxic T cells. However, optimal T cell responses may be abrogated by tightly regulated inhibitory immune checkpoints whose job is to avoid collateral damage and autoimmunity. The interplay between antigen presentation/T cell activation and T cell suppression is critically important in determining the outcome of immunotherapeutic interventions. The goal of this study is to determine the feasibility of providing the IFx-Hu2.0 injections prior to combining this agent with checkpoint blockade in future clinical trials. The goal is to initiate a self-sustaining cycle of cancer immunity, enabling it to amplify and propagate.

2.3 Potential Risks and Benefits

2.3.1. Known Potential Risks

IFx-Hu2.0 primes the immune response to a broad array of patient-specific tumor antigens. Due to the antitumor response being directed specifically against abnormal tumor proteins, there have been no reported side effects associated with this therapy. However, when breaking tolerance to tumor-associated antigens, which are 'self' antigens, there is a possibility of inducing some form of autoimmunity. Patients receiving other cancer vaccine therapies have experienced reactions including mild fever, skin reactions, sweats and chills, tachypnea and hypotension. However, the effectiveness and side effects of immunotherapies are bound by the same biological mechanisms and there may be an increased risk of autoimmunity with the IFx-Hu2.0.

2.3.2. Known Potential Benefits

The therapeutic antitumor effect of intralesional injections of pAc/*emm55* has been evaluated in horses with malignant melanoma, in C57BL/6 B16 tumor-bearing mice and companion animals with various types of cancers. Whether the plasmid DNA was formulated with water, TE buffer or *in vivo*-jetPEI® or injected with a tuberculin syringe and needle or a needleless injector, the study results support the hypothesis that pAc/*emm55*, when injected into tumor lesions *in vivo*, is expressed as an immunogenic Emm55 protein that stimulates a multi-pronged immune attack on tumor cells that is clinically beneficial. Further, no adverse events were reported in any of the 200+ animals receiving intralesional or intranodal injections of pAc/*emm55* plasmid DNA. Based on the results of these studies, Morphogenesis believes that pAc/*emm55* may have significant antitumor activity and will be well tolerated in human patients with melanoma.

3 OBJECTIVES AND PURPOSE

3.1 Primary Objective

Safety; i.e., to assess the safety, tolerability, and feasibility of vaccination with IFx-Hu2.0 as a monotherapy in patients with unresectable stage III or stage IV cutaneous melanoma.

3.2 Secondary Objective(s)

The secondary objectives include the evaluation of response rate and assessment of the antitumor immune responses induced by IFx-Hu2.0 in patients treated with this vaccine.

4 STUDY DESIGN AND ENDPOINTS

4.1 Description of the Study Design

Six male and/or female adult patients (greater than or equal to 18 years old), of any ethnicity and race, with unresectable stage III or stage IV cutaneous melanoma with accessible lesions, will be eligible for enrollment and treatment with IFx-Hu2.0. Pediatric melanoma is quite rare and the National Cancer Institute estimates that approximately 500 children are diagnosed per year. The potential for development of this product for pediatric subjects with melanoma will be evaluated after the results of this study are available.

To be eligible for this study, patients with unresectable metastatic disease must have failed, refused or been deemed not candidates for at least one form of systemic anti-PD-1-based immunotherapy as well as BRAF inhibition, if BRAF V600 mutated.

Talimogene laherparepvec (IMLYGIC®) is indicated for local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. Therefore, patients with unresectable cutaneous, subcutaneous, and nodal melanoma lesions recurrent after initial surgery must have failed, refused or been deemed not candidates for talimogene laherparepvec to be eligible for this study.

Enrollees will receive IFx-Hu2.0 at a single time point. Depending on the number of accessible lesions, a patient could receive up to three doses across three lesions (one dose per lesion). Forty millilters of peripheral blood will be collected from these patients prior to treatment administration and at the follow-up visit four weeks later. The target dose will be 100 µg of plasmid DNA per lesion injected at a final dose volume of 200 µL per lesion. To allow for the observation of any acute toxicity in the first subject enrolled and prevent any occurrence of excessive toxicities in subsequent subjects, the first subject enrolled will receive a single dose of IFx-Hu2.0. Subsequent subjects will be administered the product after at least seven days. Beyond the first subject, the maximum number of lesions to be injected at any given time point in the study phase proposed is three lesions. These samples will be used to perform complete blood counts (CBC) and clinical chemistry tests. A urine sample will be obtained for urinalysis for protein and blood at the same frequency. Blood samples will be drawn for immune response evaluation as well. Peripheral blood collections, and where feasible, as determined by PI, tumor biopsies may be obtained on the first and subsequent treatment cycles. At the end of the study period a biopsy of the lesion injected and a non-injected lesion (if applicable) will be collected. At the discretion of the PI in consultation with the Sponsor, the patient will have the option of continuing the study at three-week intervals so long as the subject under study has not progressed.

4.2 Study Endpoints

4.2.1 Primary Endpoint

The primary endpoints of this trial will be the safety and feasibility of the treatment regimen. Safety will be reported using Common Terminology Criteria for Adverse Events (CTCAE) version5.0. Feasibility will be defined as the ability to treat at least five of the six patients enrolled without dose-limiting toxicity (DLT).

4.2.2 Secondary Endpoints

The secondary endpoint consists of observing and monitoring objective response rates and, although not needed for the conclusion of this study, progression-free survival (PFS) will also be recorded when indicated. Patients who consent to additional injection cycles will be observed for toxicity over time.

4.2.3 Exploratory Endpoints

Exploratory endpoints include laboratory correlative studies including the *laboratory based* assessment of tumor-specific immunity.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Participant Inclusion Criteria

1. Histologically confirmed unresectable stage III or stage IV malignant melanoma, with accessible cutaneous lesions
2. Must have measurable disease greater than 3 mm
3. At least one injectable lesion and one lesion for biopsy at study conclusion. Lymphocyte count ≥ 500,000 cells/mL
4. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
5. Willing and able to give written, informed consent

6. If male or female of childbearing potential must be willing to use a contraceptive during the study and for six months afterward. A woman is considered to be of child bearing potential unless she as had a surgical procedure that would accomplish sterility such a bilateral tubal ligation, hysterectomy or has not had menses for the past 12 months.
7. Life expectancy greater than three months
8. To be eligible for this study, patients with unresectable metastatic disease must have failed, refused or been deemed not candidates for at least one form of systemic anti-PD-1-based immunotherapy as well as BRAF inhibition, if BRAF V600 mutated.
9. Patients with unresectable cutaneous, subcutaneous, and nodal melanoma lesions recurrent after initial surgery must have failed, refused or been deemed not candidates for talimogene laherparepvec to be eligible for this study.
10. The entry laboratory criteria for subject eligibility must be less than or equal to grade 1 adverse event levels for the parameters tested as defined by CTCAE v5.0:
    - Bone Marrow Function
        - HGB = <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L
        - WBC = <LLN - 3000/mm3; <LLN - 3.0 x 10^9/L
        - PLT = <LLN - 75,000/mm3; <LLN - 75.0 x 10^9/L
    - Coagulation Parameters
        - INR = >1 - 1.5 x ULN
        - aPTT = >ULN - 1.5 x ULN
    - Renal Function
        - Creatinine = >ULN - 1.5 x ULN
    - Liver Function:
        - Bilirubin = >ULN - 1.5 x ULN
        - ALT = >ULN - 3.0 x ULN
        - AST = >ULN - 3.0 x ULN
        - ALP = >ULN - 2.5 x ULN
        - GGT = >ULN - 2.5 x ULN

5.2 Participant Exclusion Criteria

1. Known brain metastases greater than 1 cm at screening.
2. Life expectancy of fewer than three months
3. Prior systemic anti-cancer treatment within three weeks from start of treatment (Day 0)
4. Current treatment with systemic immunosuppressive corticosteroid (greater than 10 mg of daily prednisone) doses or other immunosuppressants such as those needed for solid organ transplants. Medications needed to treat conditions such as reactive airway disease are not excluded.
5. Pregnant or lactating women
6. Presence of any uncontrolled and significant medical or psychiatric condition which would interfere with trial safety assessments
7. Treatment with any investigational product within the three weeks preceding injection
8. Immunizations for encapsulated bacteria were not given for patients who have undergone a splenectomy.
9. Serious underlying medical or psychiatric conditions, active infections requiring the use of antimicrobial drugs, or active bleeding that would make the subject unsuitable or unable to

participate in the study
10. Concurrent chemotherapy or biological therapy. Concurrent radiotherapy is allowed as long as it is not the same site as the injected lesion.
11. Uncontrolled hepatitis B, hepatitis C, or HIV infection
12. History of organ allograft transplantation

5.3 Strategies for Recruitment and Retention

This study will have a goal of six evaluable patients. It is the intent of the study team to recruit an additional two patients to be screened and enrolled if any of the existing patients are lost to follow-up, withdraw consent or exhibit disease progression.

5.4 Participant Withdrawal or Termination

5.4.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.4.2 Handling of Participant Withdrawal or Termination

Every effort will be made to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs), and unexpected adverse drug experience. Participant replacement will be permitted at the discretion of the Principal Investigator (PI).

5.5 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the PI, the IND sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the institutional review board (IRB) and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of AEs or SAEs that would warrant stopping
- Insufficient compliance with protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB and/or the Food and Drug Administration (FDA).

6 STUDY AGENT

6.1 Study Agent(s) Description

6.1.1 Acquisition

The manufacture of the drug substance (pAc/*emm55*) plasmid DNA will be conducted at Aldevron (Fargo, North Dakota). The mixing of the Investigational Product components (plasmid DNA, cationic polymer and glucose) for this Phase 1 study will be conducted at the clinical site pharmacy.

6.1.2 Formulation, Appearance, Packaging, and Labeling

The final Investigational Product is manufactured as a vaccine kit containing three vials; Vial 1- plasmid DNA, Vial 2- cationic polymer and Vial 3- glucose that are mixed at the clinical site in preparation for injection. This process is patient-specific and will occur at each clinical visit for each patient. The following table lists the final composition of Investigational Product, IFx-Hu2.0.

Component	Description	Purpose
Plasmid DNA	Mammalian expression plasmid containing *emm55* gene (pAc/*emm55*) in TE buffer (0.5 mg/mL)	Drug substance
Cationic Polymer	Polyplus-transfection *in vivo*-jetPEI® cationic polymer (0.72 mg/mL)	Excipient; cellular uptake of plasmid DNA
Glucose	5% Dextrose solution, USP	Excipient; DNA-polymer complex stability

6.1.3 Product Storage and Stability

The final Investigational Product will be injected intralesionally within four hours of the final formulation at the pharmacy. A more comprehensive product stability assessment will be part of this Phase 1 study.

6.1.4 Preparation

Described below is the preparation of IFx-Hu2.0 Investigational Product intralesional injection using a vaccine kit that contains; (1) Vial 1-pDNA (drug substance), (2) Vial 2- cationic polymer (excipient), and (3) Vial 3-glucose (excipient). These components will be provided by Morphogenesis to the Pharmacy for mixing on site as per USP <797> guidelines for single-dose containers. When possible, the preparation should be performed in an ISO 5/Class 100 environment. The vaccine kits are stored at 2-8°C until preparation is performed. All components will have accompanying Certificates of Analysis.

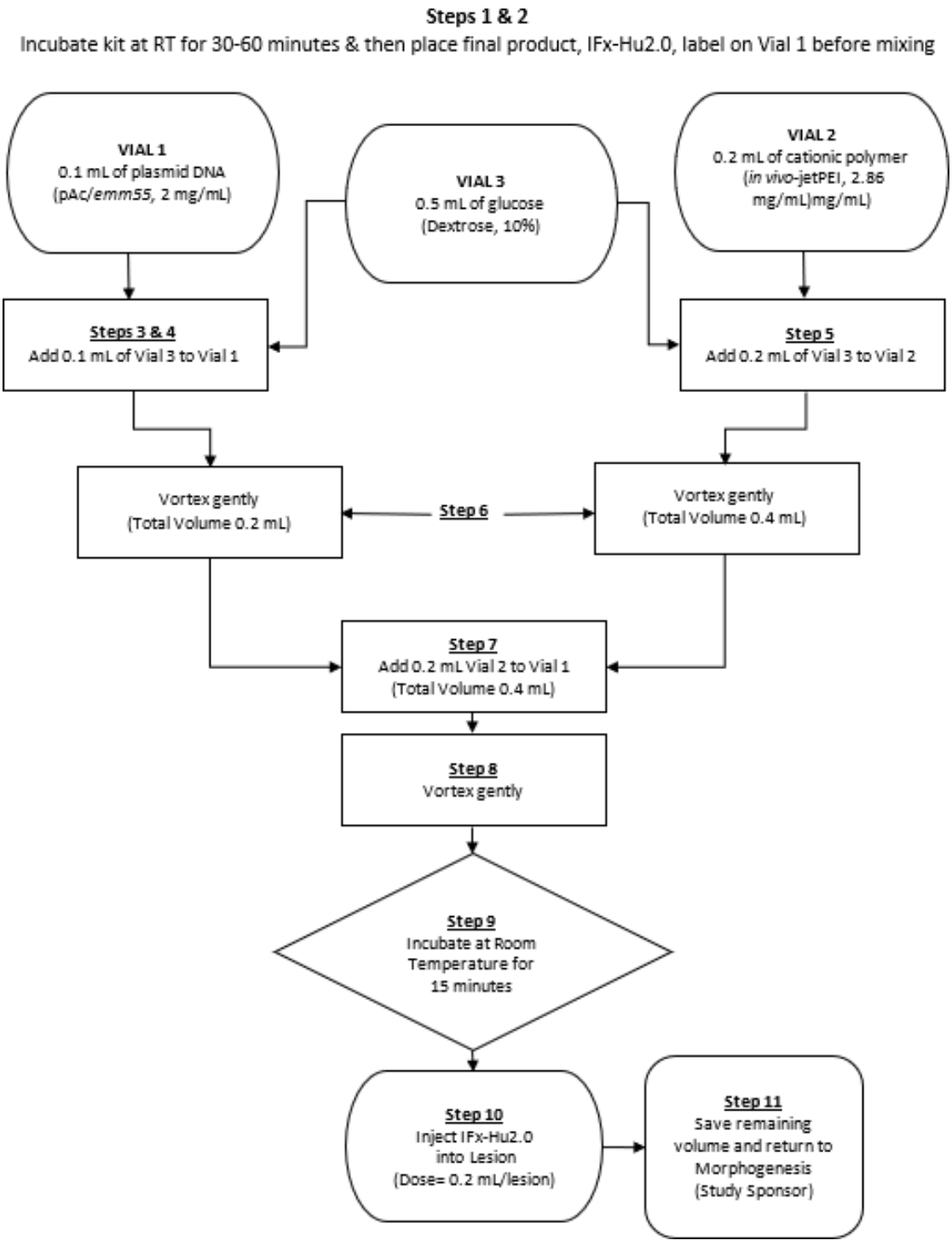
1. Incubate kit at room temperature (RT) for 30-60 minutes prior to mixing
2. Place mixed final product label, provided in Bag 1 of kit, on Vial 1
3. Remove flip cap from vials, wipe the exposed septum with alcohol as per standard clinical pharmacy procedures, and then draw up 0.1 mL of Vial 3 into a ½ mL tuberculin (TB) syringe

provided with kit

4. Place Vial 1 upright on a flat surface, and using aseptic technique, insert needle and inject Vial 3 solution into Vial 1, before removing the needle pull back on the syringe to release any pressure
5. Using a new ½ mL TB syringe, provided with kit, draw up 0.2 mL of Vial 3 and inject solution into Vial 2 using the same technique described in Steps 3 & 4
6. Vortex Vial 1 & Vial 2 individually at the "8" setting for five seconds, if this step is performed outside of the ISO 5 environment wipe vial septum with alcohol as performed in Step 3

   Note: This is a CRITICAL step to ensure complexes form properly

7. Using a new ½ mL TB syringe, provided with kit, draw up 0.2 mL of Vial 2 and inject contents into Vial 1 using the same technique described in Steps 3 & 4
8. Gently vortex Vial 1 using the same technique described in Step 6
9. Allow to incubate at room temperature for 15 minutes; the mixed solution is stable for 4 hours at room temperature after components are combined
10. The final drug product is now ready for intralesional administration using a TB syringe, supplied at the clinical pharmacy, at a dose of 0.2 mL/lesion
11. The used vials should be placed in the designated biohazard bag, provided in the kit, and returned to Morphogenesis


Steps 1 & 2
Incubate kit at RT for 30-60 minutes & then place final product, IFx-Hu2.0, label on Vial 1 before mixing
VIAL 1
0.1 mL of plasmid DNA
(pAc/emm55, 2 mg/mL)
VIAL 3
0.5 mL of glucose
(Dextrose, 10%)
VIAL 2
0.2 mL of cationic polymer
(in vivo-jetPEI, 2.86
mg/mL)mg/mL)
Steps 3 & 4
Add 0.1 mL of Vial 3 to Vial 1
Step 5
Add 0.2 mL of Vial 3 to Vial 2
Vortex gently
(Total Volume 0.2 mL)
Step 6
Vortex gently
(Total Volume 0.4 mL)
Step 7
Add 0.2 mL Vial 2 to Vial 1
(Total Volume 0.4 mL)
Step 8
Vortex gently
Step 9
Incubate at Room
Temperature for
15 minutes
Step 10
Inject IFx-Hu2.0
into Lesion
(Dose= 0.2 mL/lesion)
Step 11
Save remaining
volume and return to
Morphogenesis
(Study Sponsor)

6.1.5 Dosing and Administration

The target dose will be 100 µg of plasmid DNA per lesion injected at a final dose volume of 0.2 mL per lesion. The maximum number of lesions to be injected at any given time point in the study phase proposed is three lesions.

6.1.6 Route of Administration

Intralesional injections using 1 mL tuberculin syringes.

6.1.7 Starting Dose and Dose Escalation Schedule

The dose/lesion treated will be constant through this study: 100 µg of plasmid DNA per lesion injected at a final dose volume of 0.2 mL. However, depending on the subject, one, two, or three lesions would be injected at a time.

The subjects will receive IFx-Hu2.0 at a single time point as a monotherapy. These patients will then be observed for any dose-limiting toxicity or adverse events for up to four weeks. The maximum number of lesions to be injected in this study is three lesions.

6.1.8 Dose Adjustments/Modifications/Delays

No dose adjustments or modifications will be part of this study phase. However, the protocol will allow for delays of up to 7 business days to accommodate participant clinic visit rescheduling due to any unforeseen circumstances.

6.1.9 Duration of Therapy

Participants enrolled in the study will receive IFx-Hu2.0 at a single time point. After primary endpoint has been met (DLT), at the investigator's discretion in consultation with the sponsor, patients may receive additional doses on a 3-week cycle.

6.1.10 Tracking of Dose

Once the final Investigational Product is formulated, patient-specific labeling will be affixed showing two unique identifiers.

6.2 Study Agent Accountability Procedures

The final Investigational Product mixing involves the drug substance (pAc/*emm55* plasmid DNA in TE buffer) with the remaining components; cationic polymer and glucose. This mixing of the final Investigational Product components will occur at the clinical site pharmacy. Once the final Investigational Product is prepared, patient-specific labeling will be affixed showing two unique identifiers. Any excess product will be de-identified and returned to Morphogenesis for laboratory studies.

7 STUDY PROCEDURES AND SCHEDULE

7.1 Study Procedures/Evaluations

7.1.1 Study-specific Procedures

- Medical history through interview and/or medical records review
- Medication history to include current prescription and over-the-counter medications; a review of current medications will be part of the assessment of eligibility
- Physical examination
- Radiographic or other imaging assessments (photographs)
- Biological specimen collection and laboratory evaluations; blood draws and urine collections will be made at each of the clinical visits in addition to tissue tumor tissue collection for research purposes.
- A discussion of the results of any study-specific procedures will be provided to the participant
- Assessment of adherence to study requirements and instructions
- Collection of data on gender, race and ethnicity

7.1.2 Standard-of-care Study Procedures

Subjects will receive IFx-Hu2.0 as a monotherapy at a single time point and will be assessed for a period of four weeks. Once the four-week period expires and the toxicity/safety assessments have been completed, these patients will transition into standard-of-care or clinical trial protocols as determined by the PI and the clinical team. If the patient comes off study, PFS will need to be censored, but the time to first progression will be obtained during subsequent follow-up with the patient's consent. If the patient has a response to therapy, the patient will have the option of continuing the study at three-week intervals at the discretion of the PI in consultation with the Sponsor. In this setting, PFS will be measured in the traditional way. Where feasible, as determined by PI, tumor biopsies and peripheral blood collections may be obtained on subsequent treatment cycles.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

- Hematology: (Complete Blood Count - CBC) hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count, blood clotting tests; prothrombin time (PT) and activated partial thromboplastin time (aPTT)
- Biochemistry (Comprehensive Metabolic Profile - CMP): glucose, calcium, albumin, total protein, sodium, potassium, CO2, chloride, BUN, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), Thyroid tests (TSH and FT4)
- Urinalysis: UA with microscopic evaluation
- Serum pregnancy test, done within 24 hours prior to Investigational Product administration, and results must be available prior to administration of Investigational Product
- Human leukocyte antigen (HLA) typing

- Serology screening for HBV, HCV, HIV, HTLV, EBV and *T. pallidum* (RPR); fluorescent treponemal antibody absorption (FTA-ABS), if necessary
- Immunodeficiency Panel
- Anti-double-stranded DNA (anti-dsDNA) antibody test
- Anti-DNase B Titer, Serum

7.3 Study Schedule

7.3.1 Screening

Screening Visit (Day -36 to -1)

- Obtain informed consent of potential participant verified by signature on study informed consent form.
- Verify inclusion/exclusion criteria.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Record Concomitant Medications.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- CT as clinically indicated and/or PET scan. Photographs may be utilized for melanoma confined to the skin.
- Electrocardiogram (ECG)
- Collect blood/urine for:
    - Hematology: CBC - hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count; blood clotting tests: prothrombin time (PT) and activated partial thromboplastin time (aPTT)
    - Biochemistry: CMP - glucose, calcium, albumin, total protein, sodium, potassium, CO2, chloride, BUN, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), Thyroid tests (TSH and FT4)
    - Urinalysis: UA with microscopic evaluation
    - Serum pregnancy test: done within 24 hours prior to Investigational Product administration, and results must be available prior to Investigational Product administration
    - Human leukocyte antigen (HLA) typing
    - Serology screening for HBV, HCV, HIV, HTLV, EBV and T. pallidum (RPR); fluorescent treponemal antibody absorption (FTA-ABS), if necessary
    - Immunodeficiency Panel
    - Anti-double-stranded DNA (anti-dsDNA) antibody test
    - Anti-DNase B Titer, Serum
- Where feasible, as determined by PI, research study biopsy for histology and/or immune response assays may be collected at the screening visit or the baseline visit. PI may also elect to use archival tumor at baseline.

- In the setting of known melanoma, archival tumor tissue may be utilized to confirm the diagnosis (Moffitt or from external source).
- In this case, two 4-micron slices (positive charged slides, air dry overnight). are required for research IHC experiments under the direction of Dr. Markowitz.
- The H&E stained slide from the biopsy may be digitally scanned.
- For all portions of this protocol, fresh research biopsies will be obtained using a punch or shave biopsy technique. These samples will be placed in PBS or formalin and utilized for research purposes. The portion of the tissue divided for the PBS portion will be flash frozen and utilized for downstream assays. Dr. Markowitz will assess whether the tumor is of adequate size to split into two parts (PBS and formalin).

- Assessment and recording of ECOG Performance Status.
- Assessment and recording of Tumor Burden (lesion measurements).
- Schedule study visits for participants who are eligible and available for the duration of the study.
- Provide participants with general study procedures and instructions for clinical visits

7.3.2 Enrollment / Baseline

Enrollment/Baseline Visit (Visit 1, Day 0)

- Obtain demographic information, medical history, medication history, alcohol and tobacco use history.
- Record Concomitant Medications.
- Record vital signs, results of physical examination, other assessments.
- Collect blood/urine for:
  - Hematology: CBC - hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count
  - Biochemistry: CMP - glucose, calcium, albumin, total protein, sodium, potassium, CO2, chloride, BUN, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH)
  - Urinalysis: UA with microscopic evaluation
  - Serum pregnancy test: done within 24 hours prior to Investigational Product administration, and results must be available prior to Investigational Product administration
  - 40 mL of blood will be collected for research purposes in the laboratory of Dr. Joseph Markowitz, including immune response baseline evaluation.
- Where feasible, as determined by PI, research study biopsy for histology and/or immune response assays may be collected at the screening visit or the baseline visit.
- Administer the Investigational Product.
- Assessment and recording of ECOG Performance Status
- Assessment and recording of Tumor Burden (lesion measurements)
- Observation and recording of adverse or serious adverse events as defined by CTCAE v5.0

7.3.3 Optional Study Visits (<u>for multiple dose cycle only</u>)

(Week 4 Day 28 +/-7 business days)

- Record vital signs, results of physical examination, other assessments
- Collect blood/urine for:
    - Hematology: CBC - hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count; blood clotting tests: prothrombin time (PT), activated partial thromboplastin time (aPTT)
    - Biochemistry: CMP - glucose, calcium, albumin, total protein, sodium, potassium, CO2, chloride, BUN, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH); thyroid tests: (TSH and FT4)
    - Urinalysis: UA with microscopic evaluation
    - Serum pregnancy test: done within 24 hours prior to Investigational Product administration, and results must be available prior to Investigational Product administration
    - 40 mL of blood will be collected for research purposes in the laboratory of Dr. Joseph Markowitz, including immune response evaluation.
- Optional research study biopsy for histology and immune response assays may be collected.
- Administer the Investigational Product.
- Assessment and recording of ECOG Performance Status
- Assessment and recording of Tumor Burden (lesion measurements)
- Assessment and recording of Concomitant Medications
- Observation and recording of adverse or serious adverse events as defined by CTCAE v5.0
- CT as clinically indicated and/or PET scan (photographs may be utilized for melanoma confined to the skin)

(Week 7 Day 49 +/-7 business days)

- Record vital signs, results of physical examination, other assessments
- Collect blood/urine for:
    - Hematology: CBC - hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count
    - Biochemistry: CMP - glucose, calcium, albumin, total protein, sodium, potassium, CO2, chloride, BUN, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH)
    - Urinalysis: UA with microscopic evaluation
    - Serum pregnancy test: done within 24 hours prior to Investigational Product administration, and results must be available prior to Investigational Product administration
    - 40 mL of blood will be collected for research purposes in the laboratory of Dr. Joseph Markowitz, including immune response evaluation.
- Optional research study biopsy for histology and immune response assays may be collected.
- Administer the Investigational Product.
- Assessment and recording of ECOG Performance Status
- Assessment and recording of Tumor Burden (lesion measurements)
- Assessment and recording of Concomitant Medications

- Observation and recording of adverse or serious adverse events as defined by CTCAE v5.0

7.3.4 Final Study Visit

(Week 4 Day 28 +/-7 business days for Single Dose Cycle)

OR

(Week 21 +/- 7 business after the last dose for Multiple Dose Cycle)

- Record vital signs, results of physical examination
- Collect blood/urine for:
    - Hematology: CBC - hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count; blood clotting tests: prothrombin time (PT), activated partial thromboplastin time (aPTT)
    - Biochemistry: CMP - glucose, calcium, albumin, total protein, sodium, potassium, CO2, chloride, BUN, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH); thyroid tests: (TSH and FT4)
    - Urinalysis: UA with microscopic evaluation
    - Serum pregnancy test
    - Anti-double-stranded DNA (anti-dsDNA) antibody test
    - Anti-DNase B Titer, Serum
    - 40 mL of blood will be collected for research purposes in the laboratory of Dr. Joseph Markowitz, including immune response evaluation.
- Tumor sample biopsy of injected lesion for histology and immune response assays
- Biopsy of non-target lesion (if applicable)
- Assessment and recording of ECOG Performance Status
- Assessment and recording of Tumor Burden (lesion measurements)
- Assessment and recording of Concomitant Medications
- Observation and recording of adverse or serious adverse events as defined by CTCAE v5.0
- CT as clinically indicated and/or PET scan (photographs may be utilized for melanoma confined to the skin)

Overall Survival Status: Long Term Follow-up

- On 11/16/2020 (± 4 weeks), the survival status and subsequent anti-cancer therapy since last being seen on trial will be obtained from the EMR. Subsequent therapies will be documented from the EMR for melanoma (immune-based therapy, chemotherapy, radiation, surgery) with clinical response if available.

7.3.5 Early Termination Visit

- Record vital signs, results of physical examination
- Collect blood/urine for:
    - Hematology: CBC - hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count; blood clotting tests: prothrombin time (PT), activated partial thromboplastin time (aPTT)

- Biochemistry: CMP - glucose, calcium, albumin, total protein, sodium, potassium, CO2, chloride, BUN, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH); thyroid tests: (TSH and FT4)
- Urinalysis: UA with microscopic evaluation
- Serum pregnancy test
- Anti-double-stranded DNA (anti-dsDNA) antibody test
- Anti DNAse B Titer, Serum
- 40 mL of blood will be collected for research purposes in the laboratory of Dr. Joseph Markowitz, including immune response evaluation.

- Tumor sample biopsy of injected lesion for histology and immune response assays
- Biopsy of non-target lesion (if applicable)
- Assessment and recording of ECOG Performance Status
- Assessment and recording of Tumor Burden (lesion measurements)
- Assessment and recording of Concomitant Medications
- Observation and recording of adverse or serious adverse events as defined by CTCAE v5.0
- CT as clinically indicated and/or PET scan (photographs may be utilized for melanoma confined to the skin)

7.3.6 Unscheduled Visit

- Record vital signs, results of targeted physical examination as indicated.
- Collect blood/urine/research biopsies as indicated, at the discretion of the Investigator.
- Assessment and recording of Concomitant Medications
- Observation and recording of adverse or serious adverse events as defined by CTCAE v5.0
- Assessment and recording of ECOG Performance Status

7.3.7 Schedule of Events Table

Schedule of Events Table

Schedule of Events: (**Single dose cycle scenario**)

Procedure	Screening (Day -36 to -1)	Week 0 (D=0)	Week 4** (D=28)*	Unscheduled visit	Early Termination Visit	Long-term Follow-up[1]
Informed consent eligibility	X					X
Physical exam w/vitals	X	X	X	X	X	
Medical history	X			X	X	X
Concomitant meds.	X	X	X	X	X	
AEs/SAEs	X	X	X	X	X	
IFx-Hu2.0 dosing		X				
Blood for Immune Response Evaluation		X	X	X	X	
***Clinical labs						
CBC, CMP	X	X	X	X	X	
LDH	X	X	X	X	X	
Blood clotting tests (PT/PTT)	X		X		X	
HLA typing (if not previously reported)	X					
EBV ab	X					
Hepatitis B and C, HTLV-1 & 2	X					
HIV, RPR (FTA if necessary)	X					
Thyroid Tests (Free T4, TSH)	X		X		X	
Serum Pregnancy Test	X	X	X		X	
Immunodeficiency Panel	X					
Urinalysis	X	X	X	X	X	
Anti-double-stranded DNA (anti-dsDNA)	X		X		X	
Anti-DNAse B Titer Serum	X		X		X	

ECG	X					
Optional Tumor sample/biopsies for immune response assays	X	X	X	X	X	
Optional Tumor sample/biopsies for histology	X		X	X	X	
CT and/or PET scan (Photographs may be utilized for melanoma confined to the skin)	X		X		X	
Performance Status	X	X	X	X	X	
Tumor Burden (lesion measurements)	X	X	X	X	X	
Confirmation of histology by Moffitt (may use archival tissue)	X					
Overall Survival						X

* +/-7 business days; **Final study visit; ***Screening labs may be performed within 7 days of treatment.

[1] A long-term follow-up on 11/16/2020 (± 4 weeks) that includes the survival status and subsequent anti-cancer therapy since last being seen on trial will be obtained from the EMR. Subsequent therapies will be documented from the EMR for melanoma (immune-based therapy, chemotherapy, radiation, surgery) with clinical response if available.

Schedule of Events: **(optional multiple dose cycle scenario, sample schedule for 3 cycles)**

Procedure	Screening (Day -36 to -1)	Week 0 (D=0)	Week 4 (D=28)*	Week 7 (D=49)*	visit (21 days after last dose	Unscheduled Visit	Early Term Visit	Long-term Follow-up[1]
Informed consent Eligibility	X							X
Physical exam w/vitals	X	X	X	X	X	X	X	
Medical history	X					X	X	X
Concomitant meds.	X	X	X	X	X	X	X	
AEs/SAEs	X	X	X	X	X	X	X	
IFx-Hu2.0 dosing		X	X	X				
Blood for Immune Response Evaluation		X	X	X	X	X	X	
***Clinical labs								
CBC, CMP	X	X	X	X	X	X	X	
LDH	X	X	X	X	X	X	X	
Blood clotting tests (PT/PTT)	X		X		X		X	
HLA typing (if not previously reported)	X							
EBV ab	X							
Hepatitis B and C, HTLV-1 & 2	X							
HIV, RPR (FTA if necessary)	X							
Thyroid Tests (Free T4, TSH)	X		X		X		X	
Serum Pregnancy Test	X	X	X	X	X	X	X	
Immunodeficiency Panel	X							

Urinalysis	X	X	X	X	X	X	X	
Anti-double-stranded DNA (anti- dsDNA)	X		X		X		X	
Anti-DNAse B Titer Serum	X		X		X		X	
ECG	X							
Optional Tumor sample/biopsies for immune response assays	X	X	X	X	X	X	X	
Overall Survival								X

* +/-7 business days; **Final study visit; ***Screening labs may be performed within 7 days of treatment.

[1] A long-term follow-up on 11/16/2020 (± 4 weeks) that includes the survival status and subsequent anti-cancer therapy since last being seen on trial will be obtained from the EMR. Subsequent therapies will be documented from the EMR for melanoma (immune-based therapy, chemotherapy, radiation, surgery) with clinical response if available.

7.4 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications.

8 ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

This study will comply with all applicable regulations on IND safety reporting requirements to the FDA in accordance with 21 CFR 312.32. This study will utilize CTCAE v5.0 for toxicity and AE reporting. All appropriate treatment areas at Moffitt Cancer Center have access to a copy of the CTCAE v5.0. Careful evaluation to determine the toxicity of IFx-Hu2.0 as a monotherapy will be performed. Adverse events will be documented beginning at initiation of treatment (Day 0) and continue at each visit detailed in the study treatment schema until progression, loss to follow-up, withdrawal of consent, or death. Subjects with treatment-related toxicity will be followed for the ongoing drug-related adverse events until resolved, return to baseline, deemed irreversible by the Moffitt treating physician, or until the subject is lost to follow up, withdrawal of study consent, removal of the subject from the trial by the Moffitt treating physician, or start of a subsequent anti-cancer therapy.

8.1.1 Definition of Adverse Events (AE)

An AE is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

An ongoing or intermittent adverse event should be recorded only once, with the highest/worst grade reported for the event. This study will utilize the Common Terminology Criteria for Adverse Events version 5 (CTCAE v5) for toxicity
and adverse event reporting. A copy of the CTCAE v 5 can be downloaded from the CTEP home page http://ctep.cancer.gov/reporting/ctc.html.

8.1.2 Definition of Serious Adverse Events (SAE)

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death
- life-threatening
    - An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- inpatient hospitalization or prolongation of existing hospitalization
- results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- a congenital anomaly/birth defect in the offspring of a subject
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For reporting purposes, also consider the occurrences of pregnancy or overdose (regardless of adverse outcome) as events which must be reported as important medical events. All Grade 4 and 5 adverse events are by definition serious, and must be reported within 24 hours of the site becoming aware of the event, with follow-up reporting of outcome with the exception of grade 4 and 5 myelosuppression (including anemia, neutropenia, and thrombocytopenia that does not require hospitalization).

8.1.3 Definition of Unexpected Adverse Drug Experience

An unexpected adverse drug experience (UP) is defined by the FDA as “any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure. or, if an

investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended".

This study will use the FDA definition of UP.

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

All AEs will be assessed by the clinician using NIH-NCI-DCTD-CTEP CTCAE v. 5.0, published: June 14, 2010.

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity:

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Event

The clinician's assessment of an AE's relationship to IFx-Hu2.0 is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. To help assess, the following guidelines are used.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 Expectedness

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information described in the current IB for IFx-Hu 2.0.

8.3 Time Period and Frequency of Event Assessment and Follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes an event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring during the study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 Reporting Procedures

8.4.1 Adverse Event Reporting

All adverse events will be documented and reported to the FDA in the annual report.

8.4.2 Serious Adverse Event Reporting

The study clinician will complete an SAE Form within the following timelines:

- All SAEs, regardless of relationship, will be recorded on the SAE Form and submitted to the study sponsor within 24 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible. The study sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

8.4.3 Unexpected Adverse Drug Experience Problem Reporting

Incidents or events that meet the FDA criteria for UPs require the creation and completion of a UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents a UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 7 business days of the investigator becoming aware of the problem.

8.4.4 Reporting of Pregnancy

All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

8.5 Study Halting Rules

Administration of study agent will be halted when two grade-3 or greater AEs determined to be "possibly" or "probably" related are reported. The clinical team will notify the PI, the Peachtree Bioresearch Solutions, Inc. (PBRS) Medical Monitor (MM), and the Sponsor's designated Drug Safety Unit immediately when a second grade 3 event is reported, and the site will stop accepting new study participants. The PI will inform the PBRS MM and the Sponsor's designated Drug Safety Unit within 24 hours of this occurrence and will provide both with AE listing reports. The PBRS MM will provide

recommendations for proceeding with the study to the clinical team and study sponsor. The study sponsor will inform the FDA of the temporary halt and the disposition of the study.

8.6 Safety Oversight

Safety oversight will be under the direction of the PBRS MM and the Sponsor's designated Drug Safety Unit. The PBRS MM reviews and evaluates safety and/or efficacy data on an ongoing basis to ensure the safety of patients and the validity and integrity of data. The PBRS MM reviews SAEs, deviations, Interim analysis and final report forms, and can make the following determinations, Accepted, Acceptable with Corrective Action and Tabled. The PI shall provide a statistical report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study as often as is applicable.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with good clinical practice (GCP), and with applicable regulatory requirements.

The PI and the Clinical Research Coordinator assigned to the case will be responsible for collecting all study data and maintaining all study-related documents, including the Investigator's Study File (ISF) and patient Case Report Forms (CRFs). All CRF entries will be made into paper CRFs provided by the study site and will be verified by the PBRS CRA against both paper source documentation and electronic medical records (EMR). The patient CRFs will be secured in a locked office in the Cutaneous Research Department. The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

Regulatory documents will be reviewed and CRFs will be monitored by the PBRS Clinical Research Associate (CRA) according to PBRS Standard Operating Procedures (SOPs). Monitoring will be performed regularly for accuracy, completeness, and 100% source data verification, validation of appropriate informed consent process, reporting of SAEs, and adherence to the protocol, Good Clinical Practice (GCP) guidelines, and all applicable regulatory requirements.

To ensure adherence to the protocol, monitoring reports will be submitted to the sponsor according to the timelines specified in the PBRS Global Monitoring Plan.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical and Analytical Plans

The statistical and analytical plan was developed to assess safety in six patients.

10.2 Statistical Hypotheses

IFX-Hu2.0 may be given safely to patients with unresectable stage III/IV melanoma.

10.3 Analysis Dataset(s)

Safety Analysis Dataset: the subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of Investigational Product).

10.4 Description of Statistical Methods

10.4.1 General Approach

This is a feasibility study that is designed to evaluate the safety and the feasibility of IFx-Hu2.0 as a monotherapy in preparation for a combination trial with Keytruda® (pembrolizumab) for the treatment of unresectable stage III/IV metastatic melanoma. Safety will be assessed and reported based upon CTCAE v5.0 criteria. Feasibility will be defined as the ability to treat at least five of the six patients enrolled without dose-limiting toxicity.

The secondary endpoints consist of the objective response rate and immune response assessments. Responses will be determined using standard criteria. Other secondary endpoints will be exploratory laboratory correlative endpoints of interest. This will include immunology assessments to include but not limited to: quantity of effector T cells in the circulation and expression of the Emm55 protein within the tumor tissue. The data analysis of exploratory laboratory correlative endpoints will be descriptive. All study results will be preliminary and exploratory in nature due to the relatively small sample size of the trial.

The data analysis will mainly be descriptive. The intention-to-treat approach will be used for response to treatment data analysis of this trial. Patients who are lost to follow-up or drop out of the study for any reason prior to their scheduled Final Study Visit will be censored for any time-to-event type of endpoints at the time of their last patient contact if no relevant event has occurred by then. The overall response (CR+PR) rate will also be summarized.

10.4.2 Safety Analyses

Safety endpoints will be analyzed as summary statistics during treatment and/or as change scores from baselines such as shift tables. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA), calculated (counted once only for a given participant), presented (severity, frequency, and the relationship of AEs to study agent will be presented by System Organ Class and preferred term groupings). The information reported about each AE will be the start date, stop date, severity, relationship, outcome, and duration). AEs leading to premature discontinuation from the study and serious treatment AEs will be presented either in an independent table or a listing.

10.4.3 Baseline Descriptive Statistics

Study cohorts and groups will be compared on baseline characteristics, including demographics and laboratory measurements, using descriptive statistics.

10.4.4 Planned Interim Analyses

10.4.4.1 Safety Review

The safety analysis will be conducted on the Safety Population. The following safety parameters will be evaluated: adverse events, clinical laboratory tests, physical examinations, vital signs, ECOG performance status, ECGs, radiographic or other imaging assessments , immune safety, and immunogenicity. All safety parameters will be summarized using descriptive statistics.

- **Adverse Events**

Treatment-emergent adverse events (TEAEs) are defined as signs or symptoms that emerge during treatment or within 30 days of the last dose of Investigational Product, including those signs and symptoms that have been absent pre-treatment or that have worsened relative to the pre- treatment assessment. Any adverse event considered related to treatment will also be considered a TEAE, regardless of the elapsed time since the last dose of Investigational Product.

An immune response AE, a subset of adverse events, is defined as a clinically significant AE of any organ that is associated with Investigational Product exposure of unknown etiology and is consistent with an immune-mediated mechanism.

All AEs recorded during the study will be summarized by cohort using descriptive statistics. The incidence of TEAEs will be summarized by body system, preferred term, verbatim of adverse event, intensity (based on CTCAE Version 5.0 grade), and relationship to the Investigational Product

- **Vital Signs**

The observed vital signs at each visit and the change from baseline to each post-baseline visit will be summarized by cohort using descriptive statistics.

- **Physical Examination**

Abnormal findings in the physical examination will be summarized by dose cohort using descriptive statistics.

- **Clinical Laboratory Tests**

Clinical laboratory test values outside the normal range and clinically significant abnormal range will be flagged in the data listing. Laboratory data will be summarized by cohort using shift tables (baseline to notable post-baseline visit). The change from baseline will be summarized using descriptive statistics.

- **ECOG**

The data observed from ECOG performance status will be summarized appropriately.

- **Other Safety Evaluations**

The results of ECGs, radiographic or other imaging assessments, immune safety tests, and immunogenicity will be summarized appropriately.

10.4.5 Exploratory Analyses

The exploratory laboratory correlative endpoints of interest will be reported descriptively. A fresh tumor biopsy will be utilized to quantitatively measure the level of immune response to Emm55 expression. Subsequent

assays will be to measure immune cell subsets within peripheral blood and biopsy samples. If additional material is available after these preliminary assays, further immunological assessment of available material will be performed as suggested by our pre-clinical work.

10.5 Sample Size

The intent of this study is to enroll six evaluable patients to assess the safety of IFx-Hu2.0 as a monotherapy. The sample size has the following precision for estimation of DLT rates for estimating ranging from 0.1 to 0.5. A DLT is defined as an adverse event equal to or greater than grade 3, definitely related to the investigational agent within a 4 week period. Precision is measured by 1-sided 95% upper confidence limit on the estimated DLT rate via exact binomial distribution. For example, if no DLT is observed in patients on IFX-Hu 2.0, then the true underlying DLT rate is lower than 0.393 with 95% confidence.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Moffitt Cancer Center will maintain appropriate medical and research records for this trial in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participant's memory aids or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

To ensure that anyone who would access the patient medical record has adequate knowledge that the patient is participating in a clinical trial, it is not acceptable for the CRF to be the only record of a patient's participation in the study. CRF entries must contain information which is also recorded elsewhere in the patient's medical record.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Quality Control (QC) procedures will be implemented beginning with the Data Management (DM) provider data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site for clarification/resolution.

Following written standard operating procedures, the monitor will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

Moffitt Cancer Center will provide direct access to all trial-related sites, source data/documents, and reports, for the purpose of monitoring and auditing by the sponsor and the sponsor's designee and for inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standard

The PI will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks will be given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

When, in the judgment of the chairman of the local IRB, the Investigator, and/or the Sponsor, an amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification and IRB approval. In such cases, repeat informed consent will be obtained from subjects enrolled in the study before continued participation under the new amendment.

The FDA has recently issued guidance to address the Coronavirus Disease 2019 (COVID-19) public health emergency. If the trial participant cannot return to the study site, the consent form may be sent to the trial participant (or representative who can provide the document to the trial participant) by facsimile, email or mail, and the consent interview may then be conducted by telephone when the trial participant can read the consent form during the discussion. After the consent discussion, the trial participant can sign and date the consent form. Options for returning the document to the clinical investigator may include facsimile, a photographic image sent through electronic means, scanning the consent form and returning it through a secure email account, or posting it to a secure internet address. Alternatively, the trial participant may bring the signed and dated consent form to his/her next visit to the clinical site or mail it to the clinical investigator. The medical records for each trial participant must document the method used for obtaining consent and that informed consent was obtained prior to their continued participation in the trial. The person signing the consent form must receive a copy of the consent form. Although FDA regulations do not require the trial participant's copy to be a signed copy, FDA recommends that a copy of the signed consent form be provided. The participants may withdraw consent at any time throughout the course of the trial. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.3.3 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without the prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations.

Data will be captured in paper CRFs provided by PBRS. The CRFs will be reviewed periodically by sponsor-designated monitors throughout the conduct of the trial per the clinical trial agreement and the PBRS Global Monitoring Plan. This review will include source data verification utilizing research subjects' medical records.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at PBRS. The study systems used by clinical site research staff will be secured and password protected. The DM provider's system will store subject data in a 21 CFR Part 11 compliant electronic data management system.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Paper CRFs will be provided for use as data collection documents and maintained for recording data for each participant enrolled in the study. Data derived from source documents and reported in the CRF should be consistent with the source documents, or the discrepancies should be explained and captured in a query and maintained with the paper CRF.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be captured on paper CRFs provided by PBRS.

14.2 Study Records Retention

No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or current clinical practice requirements at Moffitt Cancer Center. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2

It is the responsibility of the site to use continuous vigilance to identify and report deviations within seven working days of identification of the protocol deviation or within seven working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

14.4 Publication and Data Sharing Policy

This study will adhere with the details set forth in the clinical trial agreement between Morphogenesis, Inc. (sponsor) and Moffitt Cancer Center (clinical site) as it pertains to the sharing and publication of clinical research data.

The International Committee of Medical Journal Editors (ICMJE) member journals has adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy and the Section 801 of the Food and Drug Administration (FDA) Amendments Act of 2007 requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine.

15 STUDY ADMINISTRATION

15.1 Study Leadership

Study leadership will be the responsibility of the PI and the clinical coordinator in collaboration with the study sponsor and/or its representative. Study leadership will meet periodically as needed.

This trial will be monitored continuously by the PI, who will be assisted by the assigned clinical trial coordinator.

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

17 LITERATURE REFERENCES

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